Remarks

Claims 1 - 21 were pending in this application. Claims 1, 6, 7, 8, 14, 17 and 20 have been amended. Support for the amendments of claims 1 and 8 can be found throughout the specification, such as on page 13, lines 18-30; and pages 17-20. Support for the amendment of claims 17 and 20 can be found throughout the specification, for example on page 16, lines 13-14. Claims 6, 7, and 14 are amended herein to correct dependency.

New claim 22 is added herein. Support for new claim 22 can be found throughout the specification, such as on page 13, lines 18-30; and pages 17-20.

Page 7 of the specification has been amended to ensure proper formatting of trademarks.

Applicants believe no new matter is introduced by the foregoing amendments. After entry of this amendment, **claims 1 - 22 are pending in this application**. Reconsideration of the pending claims is requested.

Objections to the Specification

The specification is objected to for the use of trademarks on page 7. Specifically, the Office action requests that trademarks be capitalized. Page 7 of the specification is amended herein to list trademarks in capital letters. Generic terminology was provided in the original specification on page 7. The specification is also amended on pages 17-18 to list trademarks as capital letters.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 17 and 20 were rejected under 35 U.S.C. § 112, second paragraph as allegedly the phrase "physical treatment" for depression is unclear. Applicants submit that the term "physical treatment for depression" is clear to one of skill in the art. The specification on page 16, lines 14-16 describes physical treatment for depression. However, solely to advance prosecution, claims 17 are 20 are amended herein to recite "electroconvulsive therapy, light therapy, or electromagnetic radiation," as supported in the specification, such as on page 16, lines 13-14.

Claims 6, 7 and 14 were rejected under 35 U.S.C. § 112, second paragraph as allegedly there is no antecedent basis for "botulinum toxin type A." Claims 6, 7, and 14 are amended herein to correct dependency, thereby rendering the rejection moot.

Claims 1-21 were rejected under 35 U.S.C. § 112, second paragraph as allegedly the phrase "affecting the ability" in claims 1 and 8 is unclear. Claims 1 and 8 are amended herein to recite "decreasing the ability," as suggested in the Office action, thereby rendering the rejection moot.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-15 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Murray et al., in view of Binder et al., and further in view of Carruthers et al. Applicants respectfully disagree with this rejection as applied to the claims as amended.

Murray et al. teach the treatment of spasmodic dysphonia, a neuromotor disorder that affects the voice. Murray et al. describe that treatment of subjects with botulinum toxin by injecting the toxin in the thyroidarytenoid muscle, a muscle in the neck. Injection of botulinum toxin into the neck of patients with spasmodic dysphonia resulted in reduction of voice breaks. A significant reduction in depression and anxiety was also noted. However, Murray et al. conclude that the severity of spasmodic dysphoria may be related to the changes in degree of depression (see page 616, conclusion). Thus, Murray et al. conclude that decreases in voice breaks due to the injection of botulinum toxin in the neck could result in a decrease in depression.

Murray et al. teach the injection of botulinum toxin into the thyroidarytenoid muscle in the laryngeal portion of the throat to affect the voice. Murray et al. do not suggest, nor render obvious, the injection of a neurotoxin into facial muscles. Moreover, the results presented by Murray et al. appear to suggest that it may be the improvement in voice breaks (resultant from paralysis of muscles in the neck) that lead to a decrease in depression. Murray et al. do not suggest, nor render obvious, that depression (claim 1 and claims that depend therefrom) could be treated using a neurotoxin, nor does Murray et al. suggest, or render obvious, the treatment of intermittent depression and anxiety (claim 8 and claims that depend therefrom).

Binder teaches the reduction of headache pain by injecting botulinum toxin. Binder teaches that it is preferred to introduce the toxin into extramuscular sites in the face, head and neck to reduce headache pain, as this is most efficacious. The Office action alleges that figure 1 shows injection of botulinum toxin to the muscles. For example, Binder et al. state (emphasis added):

> For example, if headache pain predominates in the frontal cranial region (see, FIG. 1), the patient may receive up to 40 units in the glabella region, and may also receive up to 40 units of the neurotoxin in the mid-forehead region. For headache pain which predominates temporally, laterally and/or suboccipitally, the initial dosage (to be administered extramuscularly) will usually be somewhat lower; e.g., about 10 units per site, followed by up to 40 units per side.
>
> For many indications (particularly vascular headaches), *extramuscular injection will be the most efficacious route of administration* as well as a route which avoids the risk of trauma to muscle tissue. Such injection may, for example, be made *subcutaneously or, preferably, perivascularly* (to produce infiltration of the neurotoxin into tissue at the target site). If possible, such injections will be made at a localized site of pain associated with the patient's presenting condition ("target site"); e.g., temporal, frontal and/or suboccipital sites in vascular headaches. Those of ordinary skill in the art will be familiar with such target sites and their pathological relationship to headache pain. For example, localized sites of pain known to be associated with the onset of migraine are the oculo-frontal-temporal area of the face and the forehead, with the former predominating in the early stages of migraine onset (see, e.g., Sjaastad, et al., Func.Neurol., 8:27-32, 1993 [fronto-temporal pain is a typical trait of classical migraine]; this reference is incorporated herein by this reference to illustrate knowledge in the art regarding localized sites of headache pain). *Common target sites are identified in FIG. 1.*

Indeed, Binder et al. disclose that the effect of botulinum toxin is not related to muscle spasm. For example, Binder states:

> The preferred target site for injection of the presynaptic neurotoxin will be in or near the or extramuscular regions, in particular, target sites of the face, cranium and neck (see, FIG. 1). Although the precise mechanism by which the method of the invention reduces headache pain is not known, *it is believed that the efficacy of the method is not necessarily dependent on whether muscle spasm or strain is present in the patient or causally related to the headache pain* experienced by the patient.

Thus, Binder does not suggest, nor render obvious, the treatment of depression (or the treatment of intermittent depression and anxiety, or the treatment of major depression) using botulinum toxin. Moreover, Binder does not suggest, or render obvious, the introduction of botulinum toxin into a facial muscle that affects the ability of a subject to scowl or frown.

Carruthers et al. teach the cosmetic use of boutlinum toxin to paralyze the depressor anguli oris muscle to alleviate downturn of a subject's mouth. Carruthers et al. do not suggest the use of a toxin to treat any emotional disorder, let alone a depression.

The legal standard applicable to determinations of obviousness based on a combination of references was reiterated by the Court of Appeals for the Federal Circuit in *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988):

> The consistent criterion for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art [citations omitted]. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** [emphasis added].

Therefore, three elements must be established in order to make a *prima facie* case of obviousness. First, the prior art must suggest, or provide the incentive for, the combination of references. Second, the combination as suggested or motivated by the art must yield the process or invention claimed. Third, the prior art must provide a reasonable expectation of success of the claimed process. At no point may the applicant's disclosure be used to satisfy the three elements. If any of these elements is absent, the rejection based on obviousness is unsupported.

In the present application, none of Murray et al., Binder, or Carruthers et al. teaches the selection of a subject having a primary emotional disorder, let alone a subject with depression (such as major depression) or the selection of a subject with intermittent depression and anxiety. Furthermore, there is nothing in the teachings of Murray et al, on the treatment of spasmodic dysphonia that would suggest combination with the teachings of Binder et al., on the treatment of headaches, or with the teachings of Carruthers et al. on cosmetic uses for botulinum toxin. Even if one were to make this impermissible combination, one would not necessarily expect that the

injection of botulinum toxin into a facial muscle would result in the alleviation of major depression, or the alleviation of intermittent anxiety and depression (which are all unassociated with voice breaks) in a subject. Thus, a *prima facie* case of obviousness has not been made.

Even if any *prima facie* case of obviousness was made, based on any combination of references, it would be rebutted by evidence of unexpectedly superior results. Results are presented in the specification that document the unexpectedly superior effect obtained using the claimed methods. In addition, submitted herewith as Exhibit A is Finzi and Wasserman, *Dermatol. Surg.* 32: 645-560, 2006 (which is the work of the inventor, published after the filing date of the subject application). This publication provides additional confirmatory evidence of the unexpected results obtained using the claimed methods. Finzi and Wasserman treated ten depressed patients with major depression with botulinum toxin A. Nine out of ten patients were no longer depressed two months after treatment. The tenth patient had an improvement in mood. Applicant submits that the documentation of the unexpected superior results obtained using the claimed methods overcome any *prima facie* case of obviousness that could be made over the impermissible combination of Murray et al, Binder and Caruthers et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-15 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Jahanshahi et al., in view of Binder and Carruthers et al.

Jahanshahi et al. teach that depression in torticollis patients is secondary to the postural abnormality of the head (see page 229, first column), and constitutes "a reaction to the disorder." Botulinium toxin was injected into the superficial neck muscles (not facial muscles) of subjects to treat torticollis (see page 229, second column). The aim of the results presented by Jahanshahi et al. was to assess "improvement of torticollis with botulinum toxin injection accompanied by improvement of depression, reduction of disability, and improvement of the negative body concept and low self esteem" (see page 229, second column). Jahanshahi et al. report that the injection of botulinum toxin into the superficial neck muscles results in straightening of the head and relief from neck pain, and reduction of depression and disability associated with head position and pain (page 231, first column). Jahanshahi et al. conclude that the improvement of

depression was a "non-specific result" and that it "provides support for the reactive nature of depression and disability in a proportion of torticollis patients" (page 231, second column). Jahanshahi et al. further discloses that neither negative body image nor low self esteem were affected by the injection of botulinum toxin into the superficial muscles of the neck (page 231, second column).

Jahanshahi et al. do not suggest, nor render obvious, the injection of a neurotoxin into facial muscles. Moreover, the results presented by Jahanshahi et al. suggest that any improvement in depression is secondary and is a result of only the straightening of the head and the resultant neck pain. Thus, Jahanshahi et al. do not suggest, nor render obvious, that depression (or major depression or intermittent depression and anxiety) could be treated using a neurotoxin.

Binder is discussed above: Binder does not suggest, nor render obvious, the treatment of major depression using botulinum toxin. Moreover, Binder does not suggest, or render obvious, the introduction of botulinum toxin into a facial muscle that affects the ability of a subject to scowl or frown.

Carruthers et al. teach the cosmetic use of botulinum toxin to paralyze the depressor anguli oris muscle to alleviate downturn of a subject's mouth. Carruthers et al. do not suggest the use of a toxin to treat depression.

None of Jahanshahi et al., Binder, or Carruthers et al. teaches the selection of a subject with depression (such as major depression), or the selection of a subject with intermittent anxiety and depression. Furthermore, there is nothing in the teachings of Jahanshahi et al, on the treatment of torticollis that would suggest combination with the teachings of Binder et al., on the treatment of headaches, or with the teachings of Carruthers et al. on cosmetic uses for botulinum toxin. Even if one were to make this impermissible combination, one would not necessarily expect that the injection of botulinum toxin into a facial muscle would result in the alleviation of major depression, or the alleviation of intermittent anxiety and depression (which are unassociated with torsion of the head or neck pain) in a subject. Thus, a *prima facie* case of obviousness has not been made.

The unexpected results obtained using the claimed methods are discussed above. Applicant submits that the documentation of the unexpected results obtained using the claimed methods overcome any *prima facie* case of obviousness that could be made over the impermissible combination of Jahanshahi et al, Binder and Caruthers et al.

Claims 16-21 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Jahanshahi et al., Binder and Carruthers et al. in view of Wagstaff et al. (abstract only). Applicants respectfully disagree with this rejection.

Jahanshahi et al., Binder and Carruthers et al. are discussed above. Wagstaff et al. teach that paroxetine (a selective serotonin reuptake inhibitor, SSRI) is effective at treating depression, obsessive-compulsive disorder, and panic disorder.

None of Jahanshahi et al., Binder, or Carruthers et al. teaches the selection of a subject with depression (claims 16-18 and 20) or the selection of a subject with intermittent anxiety and depression (claims 19 and 21), nor to they teach selection of a subject with major depression (claim 22). Furthermore, there is nothing in the teachings of Jahanshahi et al, on the treatment of torticollis that would suggest combination with the teachings of Binder et al., on the treatment of headaches, or with the teachings of Carruthers et al. on cosmetic uses for botulinum toxin, or with the teachings with Wagstaff et al. on the use of paroxetine. Even if one were to make this impermissible combination, one of skill in the art would not predict that the injection of botulinum toxin into a facial muscle would result in the alleviation of major depression or intermittent anxiety and depression in a subject, nor that that treatment of botulinum toxin for depression (such as major depression) or intermittent depression and anxiety could be used in combination with additional agents that can be used to treat depression. Thus, a *prima facie* case of obviousness has not been made.

The superior results obtained using the claimed methods are discussed above. The specification discloses that treatment with botulinum toxin was successful even in subjects that had failed treatment with other modalities, such as PAXIL® (Example 1) or ZOLOFT® (Example 2). Applicant submits that the documentation of the unexpected superior results obtained using the claimed methods overcome any *prima facie* case of obviousness that could be made over the impermissible combination of Jahanshahi et al, Binder and Caruthers et al., further

in view of Wagstaff et al. Reconsideration and withdrawal of the rejection is respectfully requested.

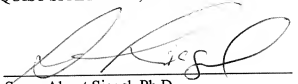
CONCLUSION

It is respectfully submitted that the present claims are in a condition for allowance. If any issues remain, the Examiner is requested to contact the undersigned attorney prior to issuance of the next Office action in order to arrange a telephone interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution and allowance of the claims.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By 

Susan Alpert Siegel, Ph.D.
Registration No. 43,121